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Ophthalmic Pathology Update

# Uveal melanoma: Ocular and systemic disease

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## Abstract

Although rare, uveal melanoma is the most common intraocular tumor in adults. Most cases arise from the choroidal layer of the uvea, displaying a discoid, collar-button, or mushroom shaped growth. Histopathologically, neoplasms are classified by the dominant cell type: spindle, epithelioid or mixed spindle cell type. The most important prognostic factors are cell type, nucleolar size, largest tumor dimension, and mitotic figures. Patient prognosis is poor when metastases occur in the liver, one of the main reasons that despite advances in the diagnosis and treatment of uveal melanoma, the mortality rate has not change significantly since 1973.

**Keywords**: Uveal melanoma, Cancer, Metastasis, Choroidal



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## Introduction

Uveal melanoma is the most common intraocular tumor in adults,[1] arising in either the ciliary body, iris, or choroid.[2] The neoplasm is most commonly manifested in the choroid (80% of all uveal melanoma) followed by the ciliary body (10%)[3] and iris (10%).[4] Although rare in adults, the malignancy is deadly when metastasized in the liver.[5]

## Clinical features

Patients often feel no symptom; however, depending on the size and location of the tumor, they may present blurred vision, visual field defects, flashes, floaters, or pain.[1] Fundus photography allows a visual classification depending on the degree of pigmentation and the shape of the lesion (nodular, flat, dome-shaped, mushroom shaped, or diffuse) (Fig. 1).[4]

Patients with choroidal masses undergo A-scan and B-scan ultrasound examinations (Fig. 2). Choroidal melanoma reveals a sharply rising and well-outlined surface signal with low to medium internal reflectivity and fast, spontaneous movement of individual spikes in A-scan ultrasonography. B-scan ultrasonography reveals an acoustically hollow mass and choroidal excavation. For tumors of at least 3 mm thickness, the combination of A-scan and B-scan ultrasonography is a diagnostic tool with greater than 95% accuracy.[6]

## Differential diagnosis

Clinically, very small tumors are frequently indistinguishable to large nevi.[2] Medium and large sized tumors are efficiently identified with modern imaging techniques, therefore only 1% of cases are misinterpreted by experienced oncologists.[2] Possible differential diagnoses include choroidal nevi, disciform degeneration, peripheral disciform degeneration, congenital hypertrophy of the retinal pigment epithelium, and choroidal hemangioma, hemorrhagic detachment of retinal pigment epithelium, melanocytoma, choroidal detachment, uveal effusion, posterior scleritis, metastatic carcinoma, choroidal osteoma, and chorioretinal granuloma.[7]

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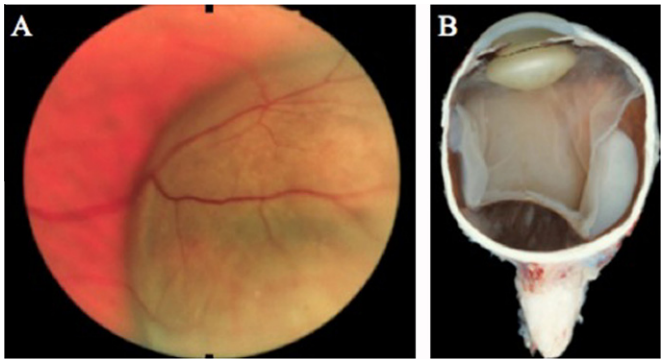


**Figure 1.** Dome-shaped choroidal melanoma: (A) fundus photography and (B) gross examination.

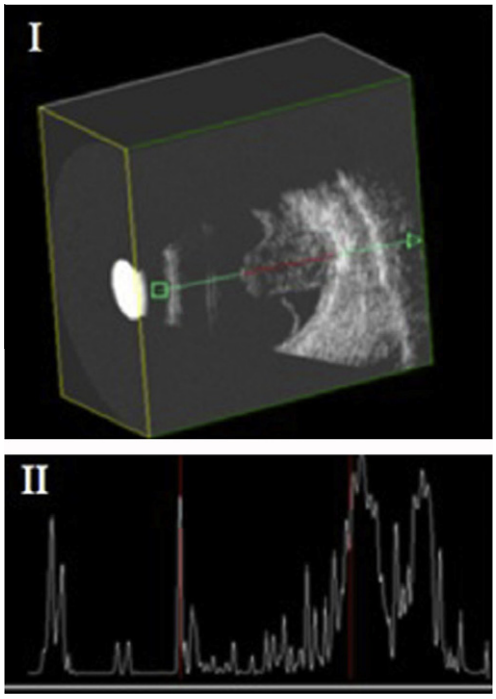


**Figure 2.** Ultrasound of a choroidal melanoma: (I) B-scan and (II) A-scan.

## Histopathology

Uveal melanoma comprises two prominent cell types: epithelioid and spindle (Fig. 3). Epithelioid cells have abundant glassy cytoplasm, a well-defined border, and abundant extracellular space between cells. Nucleoli are very large and eosinophilic within the center of the nucleus. Spindle cells are smaller, less pleomorphic, with smaller nuclei, and stacked tightly with little extracellular space. Based on their nucleus, spindle cells can be sub-categorized. Subtype A has a narrow nucleus with fine chromatin and indistinguishable nucleolus. A common feature is a longitudinal fold in the nuclear envelope resembling a chromatin streak. Subtype B has a rounder nucleus, thicker chromatin, and more prominent nucleoli.

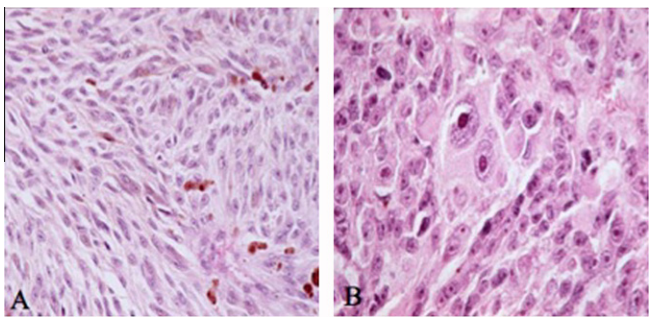


**Figure 3.** Histopathology of uveal melanoma: (A) spindle cells and (B) epithelioid cells.

Callender and colleagues[8] proposed a classification scheme based on the aforementioned histopathological features. Additionally, features such as fascicular patterns and extensive necrosis determine tumor category. The most common forms of uveal melanoma are mixed epithelioid-spindle cell tumors, representing 48% of all cases, and spindle-B cell tumors (32%). Less common are the necrotic (8%), spindle-A (6%), fascicular (5%), and epithelioid (2%) forms of the tumor.[9]

A simplified version of Callender's classification was proposed by the Armed Forces Institute of Pathology.[2,10,11] Uveal melanoma is categorized as either spindle cell or mixed spindle–epithelioid cell[10,11] with improved prediction of patient outcome.[2]

## Prognostic factors

### *Nucleoli size*

Of all cellular features, nucleoli size prevails as the best predictor of patient outcome. Although time consuming, measuring the standard deviation of nucleoli area, circumference, length, and width is reproducible, objective, and strongly correlated with patient prognosis.[12–14]

### *Tumor size*

The dimension of uveal melanoma has been proven to be relevant to patient prognosis; however, many challenges come when measuring the size of an irregularly shaped mass.[2] The most important factor to be considered is the largest measurable tumor dimension.[15–17]

### *Mitotic activity*

Mitotic figures are a strong prognostic factor, though they are scarce in uveal melanomas. A minimum of 40 high power fields at $\times$40 magnification should be evaluated for mitosis.[15–18]

### *Tumor-infiltrating lymphocytes*

Although lymphocytes are a mechanism of defense against cancer, their infiltration into the tumor is an indication of poor prognosis.[16,17,19] T-cells are more commonly seen in uveal melanoma; however, both T- and B-lymphocytes correlate with higher mortality rates.[16]

### *Tumor-infiltrating macrophage*

Macrophages can be stained using the monoclonal antibody PG-M1, which binds to the CD68 epitope. Infiltrating macrophages can be found in 83% of uveal melanoma cases[20] and is a valid prognostic factor.

### *Vascular patterns*

Neovascularization is a natural response to uveal melanoma; however, it unfortunately contributes to circulating metastasis.[17,21,22] The vessels may be arranged in a number of patterns,[17] but the strongest prognostic factor lies in the presence of loop-like patterns. Classification may be achieved through three groups: the presence of loops, presence of equivocal loops, and the absence of loops. The first group is indicative of poorer prognosis.[23]

### *Age*

The survival rates of patients decrease with age.[14,17] It is theorized that older patients have a higher risk of metastatic uveal melanoma, explaining the difference in survival rates.[2]

## Circulating malignant cells

Circulating malignant cells (CMCs) can be detected regardless of the stage of disease.[24,25] They may colonize other organs, go into a dormancy phase, and occasionally seed new CMCs into the bloodstream.[26] Their value as a prognostic factor is still a matter of debate.[27]

## Metastasis

Even though there were advances in the diagnosis and treatment of the primary tumor, the 5 year mortality rate of uveal melanoma patients remains almost unchanged since 1973.[28] The survival rates at 5, 10, and 15 years are 65%, 52%, and 46%, respectively.[29,30] Metastasis occurs mainly in the liver, which is involved in 71.4–87% of patients with metastatic disease.[31–33] The liver is the exclusive site of systemic metastasis in 40% of the patients and is often the first metastatic site in patients.[34] Unfortunately, when liver metastases are detected, treatment options are limited and life expectancy is poor, with median survival time ranging between 2.2 and 12.5 months, probably reflecting technological advances that diagnosis metastasis earlier.[33,35]

The eye does not have lymphatics and the dissemination of the primary tumor occurs through a hematogenous way.[36] Although the liver is the main site of metastasis, the cells that escape the primary tumor first encounter the capillary beds of the lungs. The reason why the liver is the main site of uveal melanoma metastasis remains unclear. It might be a mixture of two factors: reflection of homing of tumor cells to this organ or simply preferential growth and survival of these uveal melanoma cells in this microenvironment.

Uveal melanoma cells have the capacity to line, or even create vascular-like channels.[37]

### *Gene expression*

Recent studies about the metastatic process of uveal melanoma cells allowed the discovery of alterations associated with low or high risk of metastatic death.[38] Down-regulation of melanoma-specific genes including the helix–loop–helix inhibitor ID2 was found in tumors associated with a high risk of metastatic death along with a corresponding increase in E-cadherin expression,[39] as well as colocalization of E-cadherin and h-catenin to the plasma membrane, which possibly implicates a Wnt signaling pathway.

Other factors associated with metastasis are the up-regulation of insulin receptor substrate-2, fibronectin 1, and cytokeratin 18[40] and the decrease in vimentin and melanoma-specific markers, such as MelanA and CD63.[40]

Increased levels of c-Met expression in the primary tumors of patients significantly elevated the risk of those patients to develop subsequent liver metastasis.[41]

### *HGF and c-Met*

The hepatocyte growth factor (HGF), also known as scatter factor, and its corresponding receptor c-Met, play a role in specific growth of cells in the liver. After activation by HGF, c-Met is autophosphorylated on two tyrosine residues. This initiates the formation of a docking site that can recruit intracellular adapter proteins, such as growth factor receptor bound protein 2, phosphatidylinositol 3-kinase, Shc, and Src,[42] which leads to multiple downstream signaling pathways, including the Ras protein kinase pathway. These pathways give rise to the up-regulation of multiple genes and can increase cellular proliferation, cell cycle progression, protection from apoptosis, increased cellular motility, and invasive ability.[42]

### *IGF-I and IGF-IR*

Activation of IGF-IR has been shown to play a role in essential steps of the metastasis process: cellular proliferation, protection from apoptosis, migration, integrin-mediated adhesion to the extracellular matrix, and invasion of basement membranes.[43] Targeting of this pathway by using a specific inhibitor of IGF-IR tyrosine phosphorylation called cyclolignan picropodophyllin was shown to cause tumor regression in a xenograft mouse model.[44]

Phosphorylated Akt has also relates with increased metastasis in patients with uveal melanoma. It is possible that this elevated mortality rate may reflect the activation of Akt through the IGF-I pathway.[45]

### *CXCR4 and CXCL12 (chemokines)*

Tumors can express CXCR4, and this expression correlates with markers of poor prognosis.[46,47] Activation of CXCR4 by CXCL1 (stromal derived factor-1), a chemokine, has been shown to lead to a variety of intracellular signal transduction pathways and regulation of cellular survival, proliferation, migration, and adhesion.[48] Among the multiple pathways that are activated is phosphatidylinositol 3-kinase, which subsequently phosphorylates Akt. As mentioned previously, activated Akt is associated with worse prognosis in uveal melanoma and plays a role in proliferation of cells as well as migration.[49]

Recently, it has been shown that cancer cells are capable of exploiting and hijacking this system to facilitate their movement and extravasation out of the primary site and into systemic circulation.[50] It has also been hypothesized and widely believed that the CXCR4/CXCL12 mono-axis may play a critical role in guiding circulating malignant cells (CXCR4-positive cells) to organ-specific locations that actively secrete

CXCL12, such as bone, brain, lungs, and most importantly, the liver.[51]

## Conclusion

Despite the advances on diagnosis and treatment of the uveal melanoma, the survival of the patients has not improved yet. Nevertheless, the recent discoveries about the metastasis process in this disease, such as the up and down-regulation of some genes seems to be promising therapeutic targets to change the prognosis of this neoplasia.

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